

Continuous Subcutaneous Insulin Infusion Compared to Multiple Daily Injection Regimens in Children and Young People at Diagnosis of Type I Diabetes: A Pragmatic Randomised Controlled Trial and Economic Evaluation

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What is already known about this topic?

- Treatment with intensive insulin regimens [multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII)] is associated with superior glycaemic control in patients with type 1 diabetes (T1D)
- Meta-analyses and economic evaluations reporting CSII to be a cost effective treatment are based on small randomised controlled trials (RCTs) and observational data and subject to considerable modelling.
- Results of a cluster randomised trial in adults with type 1 diabetes (REPOSE) in which both groups received similar structured education did not demonstrate support for a policy of providing insulin pumps over multiple daily injections.
- An adequately powered RCT and economic evaluation was required to compare the effectiveness, safety and cost utility of CSII with MDI in children in the year following diagnosis of T1D.

What does this study add?

- Glycaemic control was suboptimal in both treatment arms at the end of the first year of T1D
- Treatment with CSII is not more clinically effective than treatment with MDI in infants, children and young people in the first year following diagnosis of T1D
- Treatment with CSII as a standalone treatment was not cost effective in infants, children and young people in the first year following diagnosis of T1D
- Parents of children treated with CSII, but not children, reported superior quality of life for their children compared to parents of participants treated with MDI.

ABSTRACT

OBJECTIVES

To compare the efficacy, safety and cost utility of CSII with MDI during the first year following diagnosis of T1D in paediatric patients.

DESIGN

Pragmatic, open, multicentre, parallel group, randomised, controlled trial.

SETTING

15 paediatric National Health Service (NHS) diabetes services in England and Wales.

PARTICIPANTS

Patients between 7 months and 15 years of age, newly diagnosed with T1D were eligible to participate. Patients with a sibling with T1D, those who took medications or had additional diagnoses that may influence glycaemic control were ineligible.

INTERVENTIONS

Participants were randomised, stratified by age and centre, to start treatment with CSII or MDI within 14 days of diagnosis. Starting doses of aspart (CSII and MDI) and glargine or detemir (MDI) were calculated according to weight and age, and titrated according to blood glucose measurements according to local clinical practice.

MAIN OUTCOME MEASURES

Primary outcome :glycaemic control (HbA1c) at 12 months. Secondary outcomes: percentage of patients in each treatment arm with HbA1c within the national target range; incidence of severe hypoglycaemia and diabetic ketoacidosis (DKA); change in height and body mass index (BMI) standard deviation score (SDS); insulin requirements (units/kg/day); partial remission rate (insulin dose adjusted HbA1c (IDAAC) < 9), PedsQL score; cost-utility based on the incremental cost per Quality-Adjusted Life-Year (QALY) gained and an NHS costing perspective.

RESULTS

294 participants were randomised and 293 included in intention to treat analyses (CSII=144 and MDI=149). At 12 months mean HbA1c was comparable with clinically unimportant differences : 60.9mmol/mol in CSII participants and: 58.5mmol/mol in MDI participants, mean difference (CSII-MDI) 2.4mmol/mol (95% -0.4 to 5.3), $p=0.09$. Achievement of HbA1c <58mmol/mol was low: 66 (46%) of 143 CSII participants and 78 (55%) of 142 MDI participants, RR 0.84 95%CI (0.67 to 1.06). Incidence of severe hypoglycaemia and DKA were low in both groups. Sixty-eight adverse events (AEs) (14 serious) were reported during CSII treatment and 25 AEs (8 serious) during MDI treatment. Parents, but not children, reported superior PedsQL scores for those treated with CSII. CSII was more expensive than MDI by £1,863 (95% CI £1,620 to £2,137) per patient with no additional QALY gains, -0.006 (95% CI -0.031 to 0.018).

CONCLUSION

During the first year of T1D no clinical benefit of CSII over MDI was identified in the UK setting and treatment with either regimen was suboptimal in achieving HbA1c thresholds. CSII was not cost-effective.

TRIAL REGISTRATION

International Standard Randomised Controlled Trial Number registry (ISRCTN29255275) and European clinical trials database (EudraCT number: 2010-023792-25).

Type I diabetes (T1D) is a common, chronic disease of childhood, affecting approximately 26,000 infants, children and young people in the United Kingdom.¹ Treatment requires administration of subcutaneous insulin in doses calculated according to carbohydrate consumption, physical activity and blood glucose measurements. During childhood and adolescence, poor glycaemic control is associated with impaired memory,² poorer cognitive outcomes,³ an increased risk of depression⁴ and poor growth.⁵ In the longer term, vascular complications lead to blindness, renal failure, premature heart disease, stroke and amputation.⁶ The risk of developing complications is related to glycaemic control, and is lower in patients treated with intensive insulin treatment regimens: multiple daily injections (MDI) and continuous subcutaneous insulin infusions (CSII).⁷ There is no cure for T1D so optimal treatment is essential to enable the best possible quality of life (QoL) and effective use of healthcare resources while minimising the risk of complications.

A meta-analysis of six randomised controlled trials (RCTs) involving 165 children reported a modest benefit of CSII treatment on glycaemic control (HbA1c -0.24%, 95% CI -0.41 to -0.07)⁸ albeit below the threshold associated with better clinical outcomes (0.5%),⁷ but no difference in the risk of severe hypoglycaemia or diabetic ketoacidosis (DKA).⁸ However, key limitations need to be considered when interpreting these results. First, in five of the included RCTs the observation period was insufficient (\leq seven months) for the effects of treatment fatigue to be observed, and may not have been long enough for patients to become fully competent in the use of CSII. Second, the use of isophane insulin in the MDI arm of five of the studies included, limits the generalisability of the results to modern regimens using long acting insulin analogues. Third, five of the six RCTs randomised patients with established T1D treated with MDI to continue MDI treatment or change to CSII. This introduces selection bias: patients in whom MDI treatment is satisfactory are less likely to be invited or to consent to participate than those in whom treatment is inadequate. A more recent study in which MDI treated patients with established T1D, in whom treatment was inadequate, were randomised to either continued MDI treatment for six months or to change to CSII, reported beneficial effects of CSII on QoL, but no effect on HbA1c.⁹

In a small RCT of newly diagnosed patients observed for two years, there was no difference in glycaemic control or adverse events (AEs) between treatment arms.¹⁰ Finally, at the start of CSII therapy there is a period of intense education and frequent contact with diabetes health care professionals, which may influence glycaemic control independently of CSII treatment in those with established diabetes. When adult patients with T1D and poor glycaemic control were randomised to treatment with CSII or MDI and given equivalent education in the REPOSE study, no additional benefit from CSII was identified.¹¹

Observational studies of national paediatric databases from the United States, United Kingdom, Germany and Austria report an association between CSII treatment and superior glycaemic control^{12,13} with only a modest effect. CSII use is lower in patients from ethnic minorities and those with greatest socioeconomic deprivation.¹⁴⁻¹⁶ Given that glycaemic control and severe hypoglycaemia are independently related to ethnicity and deprivation,¹⁴⁻¹⁶ there is a risk of bias, inherent to observational data, in estimates of the effect of CSII in these studies.

The cost of T1D to the NHS is significant, with estimates ranging from £1bn to £1.8bn a year^{17,18} and expected to be nearly 2% of total NHS expenditure over the next two decades.¹⁷ A cost effectiveness analysis from the REPOSE study concluded that routine use of CSII in adults, without an immediate clinical need, would not be cost effective.¹⁹ The economic evidence, which indicates more expensive treatment with CSII to be cost-effective in paediatrics,^{20,21} relies on data from these limited trials and extensive modelling. Use of CSII in paediatric practice increased from 14% of patients in 2011 to 28% in 2015-2016.¹ The widespread adoption of CSII, with little evidence of treatment superiority compared to MDI, requires an adequately powered RCT, designed to address areas of bias inherent in previous studies. We therefore conducted the SCIPI trial (SubCutaneous Insulin: Pumps or Injections?), in which we recruited paediatric patients newly diagnosed with T1D, and compared outcomes after one year.

METHODS

Patient and Public Involvement

Study design, delivery and data interpretation was undertaken in close discussion with patients and their families. Young people were consulted on the design of the study including impact of participation, outcome measures and study materials. Parents of children and young people with T1D were members of the Trial Management Committee and Trial Steering Committee and advised on recruitment strategy. Study results and their significance to patients and their families were discussed in detail with parent contributors.

Trial Design

The study protocol has been previously published.²² In brief, we conducted a pragmatic, multicentre, open label, parallel group, randomising participants to CSII or MDI to compare efficacy, safety and cost utility. The study was conducted in paediatric diabetes services experienced in use of CSII, in nine university and six local hospitals within the NHS in England and Wales. The study protocol (supplementary appendix) was approved by the Liverpool East Research Ethics Committee, UK, reference 10/H1002/80.

An internal pilot tested study feasibility, and the standard deviation used to inform the power calculation. A consent rate of $\geq 50\%$, with no differences likely to be of clinical significance in demographic criteria for age, ethnicity, gender and deprivation score between those that consented and declined to participate was required to proceed to the full study.

Study sites were selected on the basis of the availability of a core set of experienced staff who had completed a recognised insulin pump therapy course and had their competencies assessed and authorised.

Participants

Patients between 7 months and 15 years of age, newly diagnosed with T1D were eligible to participate. Patients with any of the following characteristics were ineligible: previous treatment for T1D, haemoglobinopathy, co-existing conditions or treatment likely to affect glycaemic control, psychological or psychiatric disorder, an allergy to a component of insulin aspart /determir (Novo Nordisk, Gatwick, UK) or insulin glargine (Sanofi, Guildford, UK), a sibling with T1D. Patients with

thyroid disease or coeliac disease were eligible if thyroid hormone concentrations or coeliac antibodies demonstrated good adherence to treatment.

Patients and carers were given written, age appropriate, study information at diagnosis of T1D, supplemented by a video presented by participants and parents from February 2014. Written, informed consent, and where appropriate assent, was obtained from carers and participants.

Randomisation

Patients were randomised to treatment with CSII or MDI using 1:1 web-based block randomisation stratified by age (7 months to <5 years, 5 years to <12 years, ≥12 years) and treating centre.

Participants were recruited by members of their local diabetes service and research nurses trained in the recruitment of paediatric patients. Parents and carers, and when appropriate patients, were invited to share reasons for declining to participate.

Procedures

The following baseline data, from the time of diagnosis of T1D, were collected: blood pH, blood glucose, HbA1c, thyroid function tests, anti-islet cell and anti-GAD antibodies, tissue transglutaminase or other antibody test for coeliac disease measured per local practice prior to consent and did not form part of the study protocol. All participants completed a structured educational program, which covered the syllabus outlined by the International Society for Paediatric and Adolescent Diabetes.²³ This included type 1 diabetes, the use and administration of insulin, hyperglycaemia and correction of dose, hypoglycaemia symptoms and treatment, exercise, sick day rules, carbohydrate counting, the benefits of maintaining optimal glycaemic control for long-term health and blood glucose monitoring. The number of education sessions was recorded to ensure parity across treatment arms. All participants received training on the use of MDI regimen and the Expert glucometer with participants randomised to CSII receiving additional training in the use of CSII. All advanced pump features were taught, used and regularly reviewed.

Randomised treatment started within 14 days of diagnosis of T1D. Baseline height and weight were documented on the day randomised treatment started. Participants randomised to CSII were treated

with insulin aspart, and those randomised to MDI with the short acting insulin analogue insulin aspart and a long acting insulin analogue, either insulin glargine or detemir, according to local clinical practice. Insulin doses were calculated according to weight and age (see study protocol, supplementary appendix), and titrated against blood glucose readings according to local protocols. Participants in both treatment arms used a glucometer which included a 'bolus wizard', which calculated insulin doses according to blood glucose readings and carbohydrate consumption. Study visits coincided with clinic appointments at three, six, nine and twelve months. At each visit the following data were collected: HbA1c, AEs, height, weight, concomitant medications and insulin usage from prescriptions, glucometer and insulin pump downloads (CSII) and patient kept records (MDI). Participants and carers documented home episodes of severe hypoglycaemia²⁴ and DKA in a diary. Treatment diaries and telephone logs were assessed at each study visit for any treatment related AEs and related serious AEs (SAEs).²⁵

In addition to self-reporting, local hospital databases were interrogated at each clinical assessment to ascertain whether the participant had been treated for a related SAE in the preceding three months. AEs were classified according to relationship with the injection device, glucometer, insulin, errors in insulin administration or incidental illness.

The Health Utilities Index (HUI) questionnaire²⁶ was administered at baseline and each study visit, and the diabetes module of PedsQL²⁷ was completed at six and twelve months.

Resource use was measured using questionnaires and by accessing prescription records and electronic patient-linked information costing systems. These included the purchase of pumps or MDI injection devices and associated consumables, insulins, and contact with healthcare services including family doctors, school nurses, hospital inpatient, outpatient, and Emergency Department attendances.

Data were collected on paper-based case report forms and questionnaires and entered centrally at the clinical trials unit into MACRO (InferMed Ltd, London, UK), a compliant clinical data management system. Bespoke software was developed to receive data downloaded from glucometers and pumps.

Outcome Measures

The primary outcome measure was HbA1c twelve months following diagnosis of T1D. Blood samples were analysed locally and centrally at Alder Hey Children's Hospital, Liverpool using the Siemens DCA Vantage HbA1c analyser. Within batch precision is <6% and between batch precision is <8%. A limits of agreement analysis was undertaken for measurements made in different laboratories and by 'point of care' (POC) methods.²⁸ Sensitivity analyses were performed using samples analysed centrally only, POC only and POC in preference to central if both were available. Secondary outcome measures were: the percentage of patients in each treatment arm with HbA1c within the national target range;²⁹ incidence of severe hypoglycaemia (hypoglycaemia associated with altered consciousness), and DKA; change in height and body mass index (BMI) standard deviation score (SDS); insulin requirements (units/kg/day); partial remission rate defined as insulin dose adjusted HbA1c (IDAAC) $< 9(\text{HbA1c } (\%) + [4 \times \text{insulin dose (U/Kg/24h)}])$ ³⁰, PedsQL score; cost-utility based on the incremental cost per Quality-Adjusted Life-Year (QALY) gained.

Statistical Analysis

SCIPI was designed as a superiority trial assuming a null hypothesis of no difference. To detect a difference in means of 0.5% (or 5.46 mmol/mol conversion),³¹ the minimum difference generally considered to be clinically meaningful,⁷ with common standard deviation of 1.50 using a two group t-test with a 0.05 two-sided significance level, 286 participants (143 per group) were required to achieve 80% power. To allow for 10% loss to follow up, the recruitment target was increased to 316 participants (158 per group).

At the time of designing the trial the association between HbA1c at diagnosis and longer term outcomes was speculative. At baseline HbA1c, reflects blood glucose in the previous three months when the child is untreated and including baseline values may add to variation therefore the sample size calculation was based on HbA1c at 12 months follow up.³² Two exploratory analyses were considered to include HbA1c measured at baseline as a continuous explanatory variable.

The ITT principle was used for the primary analysis such that all randomised participants in whom the outcome was observed were included in the group to which they were randomly allocated. A 0.05 level of statistical significance and 95% confidence intervals are used throughout. The statistical and health economic analysis plans³³ were developed prior to analysis and are available as supplementary material. Analyses were conducted using SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA) or Stata (version 13; StataCorp LLC, College Station, TX, USA). Independent statisticians from within the clinical trials unit produced and monitored the randomisation lists, statistical analysis plan³³ and undertook quality control via independent programming for the primary outcome and safety analyses. Blinding of the trial statistician was not possible, however inclusion of each participant within each analysis set was determined prior to use of allocation information.

The primary outcome, HbA1c 12 months following randomisation, used least-squares regression adjusted for age category and centre as a random effect. Due to the expected low incidence of events secondary binary outcomes are presented as unadjusted relative risks. A per protocol analysis was undertaken for the primary outcome to check robustness of conclusions to major pre-specified protocol deviations (see Table S2). BMI and height were standardised using WHO growth standards^{34,35} and analysed using analysis of covariance with respective baseline measures, age-strata and treatment group included as covariates in the model with centre fitted as a random effect. Insulin requirements (units/kg/day) were calculated to reflect insulin use over a 4 week period and were then analysed as per growth outcomes without baseline measure reflecting the absence of insulin use in this untreated population prior to randomisation. PedsQL overall score (0-100) at 12 months was calculated as per PedsQL guidelines according to the age-specific questionnaires used and were then analysed as per growth outcomes. Partial remission rate at 12 months (defined as insulin dose adjusted HbA1c (IDAAC) < 9) was calculated using HbA1c, weight and daily insulin dose and analysed as per binary outcomes. A safety analysis was conducted on AE data according to the method of

insulin delivery at the time of the event. The incidence density rate (IDR) was used to quantify the number of patients with at least one new case per population at risk in a given time period. The denominators are the sum of the person-time in years for each treatment group (accounting for treatment switches) of the at risk population. For the cost-utility analysis, UK HUI2 tariffs²⁶ were used to estimate utilities and trapezoidal rule to calculate QALYs. Resource use was costed from the perspective of the NHS using the National Tariff and other national unit costs. The ratio of the differences between intervention groups in costs and QALYs was compared with the NHS cost-effectiveness threshold of £20,000 per QALY. The joint uncertainty in costs and QALYs was considered through 10,000 Bootstrap replicates (bias corrected and accelerated). A lifetime modelled extrapolation was only planned if differences were apparent in HbA1c between intervention groups at 12-months.

STUDY FUNDING

The UK National Institute for Health Research Health Technology Assessment Programme funded the study. Roche provided insulin pumps and consumables at a 25% discounted cost. Insulin pumps from other manufacturers were also used at the discretion of the treating clinician.

RESULTS

Internal Pilot

Recruitment data from the internal pilot study showed acceptable consent rates, no evidence of patient selection bias and supported the parameters used in the sample size calculation. The oversight committees recommended progression to the full study. Data from patients recruited to the internal pilot study were included in the full study.

Study Participants

Between May 2011 and January 2016, 976 patients diagnosed with T1D were assessed for eligibility in 15 study centres. Of 689 patients who were eligible and approached for consent, 294 (42.7%, CSII=144, MDI=149) consented to participate. One patient withdrew before starting their

randomised treatment. The sample size calculation was inflated to 316 participants to allow for 10% attrition, the observed attrition was lower such that the trial was stopped following 294 randomisations to provide the numbers required to achieve 80% power. (Figure 1). Of patients invited to participate in SCIPi that declined to be randomised, 66% (259/395) stated they and/or their parent/carer had a strong preference for MDI and 9% (39/395) because they had a strong preference for CSII.

Eighty (91/114) percent of participants and 92% (130/142) of parents/carers randomised to CSII received their favoured preferred treatment, compared to 37% (41/112) of participants and 28% (42/148) of parents/carers randomised to MDI ($p<0.0001$).

Age, gender, ethnicity and deprivation score did not differ between those who consented to participate and those who declined (Table S1 supplementary material), or between treatment arms (Table 1).

Table 1: Baseline characteristics of the participants

	CSII N=144	MDI N=149	Total N=293
Age at randomisation (years):			
Median (IQR)	9.9 (5.7 to 12.2)	9.4 (5.8 to 12.5)	9.8 (5.7 to 12.3)
Age category:			
7mths to <5 years: N (%)	33 (22.9)	32 (21.5)	65 (22.2)
5 to <12 years: N (%)	71 (49.3)	76 (51)	147 (50.2)
12 to 15 years: N (%)	40 (27.8)	41 (27.5)	81 (27.6)
Gender:			
Female: N (%)	71 (49.3)	69 (46.3)	140 (47.8)
Male: N (%)	73 (50.7)	80 (53.7)	153 (52.2)
Ethnicity*: [N missing data]	[1]	[3]	[4]
Asian or Asian British	3 (2.1%)	3 (2.1%)	6 (2.1%)
Black or British Black	0 (0%)	3 (2.1%)	3 (1%)
British White	124 (86.7%)	118 (80.8%)	242 (83.7%)
Indian	2 (1.4%)	2 (1.4%)	4 (1.4%)
Mixed	4 (2.8%)	6 (4.1%)	10 (3.5%)
Other White	6 (4.2%)	8 (5.5%)	14 (4.8%)
Other	3 (2.1%)	2 (1.4%)	5 (1.7%)
Pakistani	1 (0.7%)	4 (2.7%)	5 (1.7%)
Deprivation score continuous*: [N missing]	[7]	[6]	[13]

data]			
Median (IQR)	19.4 (8.9 to 37.9)	14.7 (7.8 to 31.8)	17 (8.4 to 35.8)
BMI* SDS: [N missing data]	[20]	[17]	[37]
Mean (SD)	0.2 (1.3)	0.1 (1.4)	0.1 (1.3)
Height SDS: [N missing data]	[20]	[17]	[37]
Mean (SD)	0.3 (1.1)	0.3 (1.1)	0.3 (1.1)
HbA1c (mmol/mol): [N missing data]	[12]	[18]	[30]
Mean (SD)	104.6 (24.4)	102.6 (26.7)	103.6 (25.5)
Blood glucose (mmol/L): [N missing data]	[3]	[3]	[6]
Mean (SD)	26.8 (9.2)	26.9 (10)	26.9 (9.6)
Blood pH: [N missing data]	[17]	[16]	[33]
Mean (SD)	7.3 (0.2)	7.3 (0.1)	7.3 (0.2)

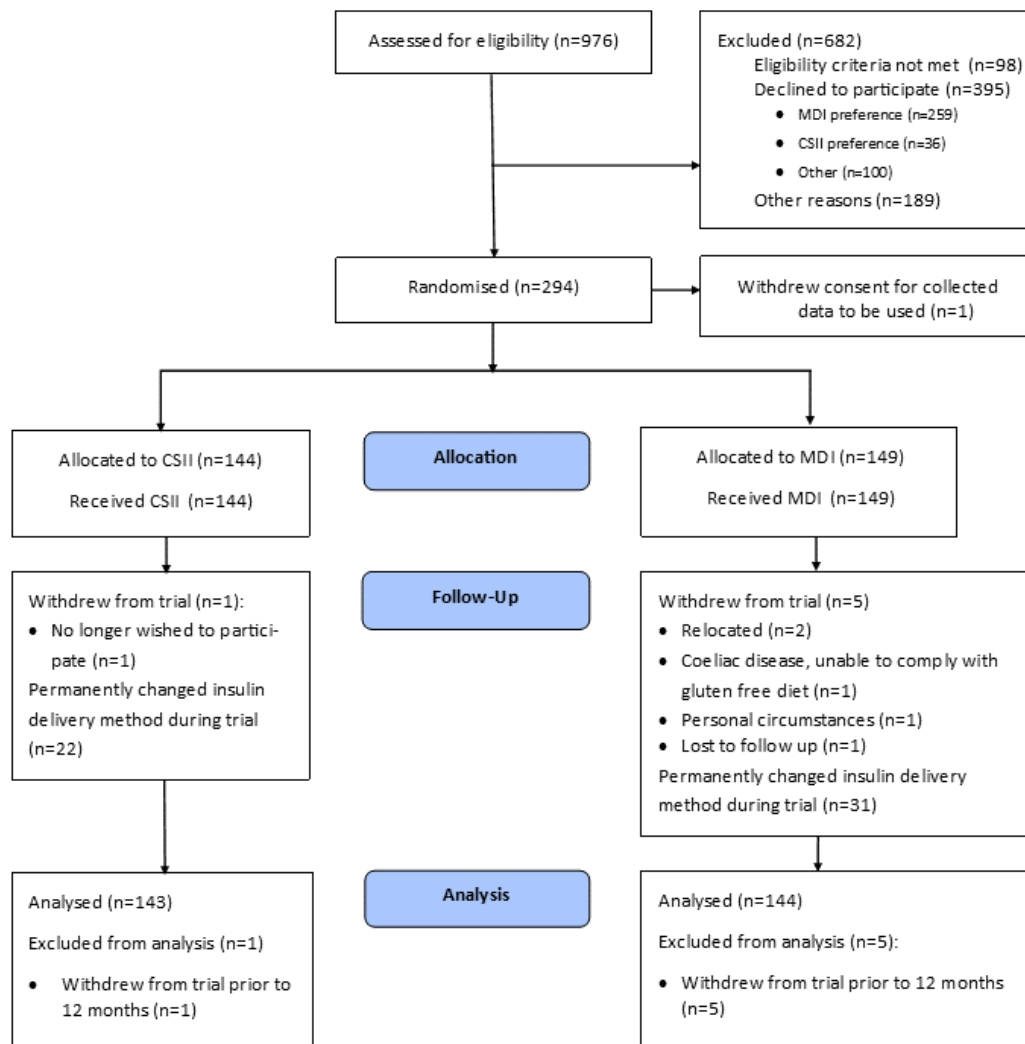
* Ethnicity was self-reported.

BMI: Body mass index is the weight in kilograms divided by the square of the height in meters.

Deprivation Score 0 to 100 with 100 indicating greater deprivation.

IQR: Inter quartile range, SD: Standard deviation.

Figure 1: CONSORT diagram illustrating patient flow from diagnosis to completion of the study protocol



Adherence to the Protocol

A CONSORT diagram illustrating the pathway of patients from diagnosis to study completion is given in Figure 1. Retention and adherence data are reported in Figure S1 and Table S2, supplementary material. All participants received their allocated interventions other than one participant who withdrew consent immediately following randomisation. Twenty-one of 144 participants (14.6%) switched from CSII to MDI, and 30 of 149 participants (20.1%) switched from MDI to CSII. Primary outcome data were available for 97% (285/293) of participants. Primary and secondary outcome measures are provided in Table 2.

Table 2: Primary and secondary outcome measures

Continuous Outcome	Adjusted mean CSII (95% CI) N=144	Adjusted mean MDI (95% CI) N=149	Adjusted mean difference (CSII-MDI), (95% CI)	p-value
HbA1c (mmol/mol) at 12 months: Intention-To-Treat (ITT)*#	n=143 60.9 (58.5 to 63.3)	n=142 58.5 (56.1 to 60.9)	2.4 (-0.4 to 5.3)	0.09
HbA1c (mmol/mol) at 12 months: Per Protocol (PP)#	n=87 60.2 (56.4 to 63.9)	n=66 59.3 (55.3 to 63.2)	0.9 (-3.2 to 5.0)	0.67
Change in BMI SDS*§	n=122 0.6 (0.8)	n=122 0.5 (0.8)	0.1 (0 to 0.3)	0.13
Change in height SDS*‡	n=122 -0.1 (0.5)	n=122 0 (0.4)	-0.1 (-0.2 to 0)	0.10
Insulin requirements (units/kg/day)*#	n=87 0.7 (0.2)	n=64 0.6 (0.3)	0.1 (0.0 to 0.2)	0.01
Binary Outcome	Number (%) CSII N=144	Number (%) MDI N=149	Relative risk (CSII/MDI), (95% CI)	p-value
Participants with HbA1c <58mmol/mol*	n=143 66 (46.2)	n=142 78 (54.9)	0.84 (0.67 to 1.06)	0.16
Participants with HbA1c <48mmol/mol*	n=143 22 (15.4)	n=142 29 (20.4)	0.75 (0.46 to 1.25)	0.28
Incidence of Severe Hypoglycaemia*	n=144 6 (4.2)	n=149 2 (1.3)	3.1 (0.6 to 15.1)	0.17
Incidence of Diabetic Ketoacidosis*	n=144 2 (1.4)	n=149 0	5.2 (0.3 to 106.8)	0.24

Partial remission (IDAAC<9)*	n=86	n=64		
	21 (24.4)	21 (32.8)	0.74 (0.45 to 1.24)	0.28

*Intention to treat analysis.

Adjusted for randomisation strata (age category – fixed effects; centre – random effects).

\$ Adjusted for randomisation strata (age category – fixed effects; centre – random effects) and baseline BMI SDS.

¥ Adjusted for randomisation strata (age category – fixed effects; centre – random effects) and baseline height SDS.

BMI: body mass index.

IDAAC: Insulin dose adjusted HbA1c.

Primary Outcome

The treatment arms were comparable for HbA1c at 12 months with differences between the treatment arms being small and unimportant in the ITT analysis (CSII 143, MDI 142), Table 2, (see Table S3, supplementary material, for full primary outcome results split by age group) or the per protocol analysis. Sensitivity analyses demonstrated robustness of results to the measurement of HbA1c at central laboratory and POC. (Table S4, supplementary material). Details of HbA1c by age group and at each time point are given in Figure S2, supplementary material. The study was not powered to detect differences in glycaemic control between age groups. However, the observed HbA1c values were generally lower for the youngest and oldest age groups during treatment with MDI, although there is a lot of uncertainty when comparing across groups. A Forest plot demonstrating stability of treatment effect over time is provided (Figure S3, supplementary material), despite changes in NHS diabetes care during the SCIP trial. Forest plots of the primary outcome split by subgroup (Figure S4, supplementary material) also show consistency of treatment effect across age groups and SCIP centres.

The trial was powered to detect a difference between groups in their measures at 12 months unadjusted for baseline values. The prognostic value of significance of HbA1c at diagnosis of T1D was not well recognised at the time SCIP opened to recruitment. Two exploratory analyses were considered to include HbA1c measured at baseline as a continuous explanatory variable (see Table

S5, supplementary material). These results did not alter the SCIP study conclusions for CSII compared with MDI at 12 months [adjusted mean difference between treatment groups (CSII – MDI) 2.9; 95% CI –0.02 to 5.9], but did suggest the importance of early baseline values for 12-month measurements (HbA1c level baseline coefficient estimate 0.07; standard error 0.03; 95% CI 0.01 to 0.13).

Another exploratory analysis considered the impact of deprivation (see Table S7, supplementary material). While there was an association of higher baseline HbA1c values and of higher deprivation scores being associated with higher HbA1c at 12 months the conclusions remained unaltered: adjusted mean difference in HbA1c at 12 months between treatment groups (CSII-MDI) 2.9 mmol/mol 95% CI (-0.02, 5.9) and (CSII-MDI) 2.2 mmol/mol 95% CI (-0.7, 5.0) respectively.

Secondary Outcomes

Secondary outcomes were analysed as per ITT (Table 2).

There was no difference in the number of participants achieving HbA1c targets (<58mmol/mol, the target until August 2015, and <48mmol/mol, the target set in August 2015²⁸).

Change in BMI and height SDS were similar between treatment arms.

Insulin dose data were available for 52% of participants (CSII 87/144, MDI 64/149). Insulin requirements were higher in those treated with CSII (0.1 units/kg/day, 95% CI 0.0 to 0.2, p = 0.01), primarily in the oldest participants. The basal bolus ratio for patients treated with CSII, across the lifetime of the study, was 0.8 starting from 0.73 at 1 month fluctuating up and down throughout the course of the trial ending at 0.67 at 12 months. (Figure S5 and Table S6, supplementary data). Similar data for MDI are not as robust as they depend on patient reporting.

Eight episodes of severe hypoglycaemia were reported (CSII=6, MDI=2) and two episodes of DKA (CSII=2, MDI=0).

The safety dataset reports events were categorised according to the treatment the participant was receiving at the time of the AE and takes into account temporary or permanent switches in the method of insulin delivery. The total number of events experienced and the number of participants

experiencing at least one event are provided along with the Incident Density Ratio (IDR), defined as the number of patients with at least one new AE per population at risk in a given time period.

Fifty-four AEs were reported in 36 participants treated with CSII at the time of the AE, 29 of which were related to the insulin pump, with IDR of 25.0 participants with at least one event per 100-person-years. Seventeen AEs were reported in sixteen participants (IDR 10.5 participants) treated with MDI at the time of the AE, two of which were related to injection device.

Fourteen SAEs were reported in nine participants (IDR 6.2 participants) treated with CSII at the time of the SAE and 8 SAEs in 8 participants (IDR 5.3 participants) treated with MDI at the time of the SAE.

Adverse event data are summarised in Table 3.

Patients randomised to CSII had twice as many T1D related Emergency Department visits and inpatient stays (122 visits made by 35/144 patients), than those randomised to MDI (60 visits made by 25/149 patients); a mean difference of 0.4 per patient (95% CI 0.1 to 0.9). Reasons for those that were recorded as SAEs are provided in Table 3.

Table 3: Serious adverse events and adverse events

		CSII 144.1 Total person years 144 patients	MDI 151.9 Total person years 149 patients	CSII 144.1 Total person years 144 patients	MDI 151.9 Total person years 149 patients

Category	Description	Adverse Events				Serious Adverse Events*			
		Events	Patients (IDR)	Events	Patients (IDR)	Events	Patients (IDR)	Events	Patients (IDR)
All	Diabetic Ketoacidosis	2	2 (1.4)	0	0 (0)	2	2 (1.4)	0	0 (0)
	Insulin administration error	2	2 (1.4)	5	5 (3.3)	2	2 (1.4)	3	3 (2)
	Pump Failure	4	3 (2.1)	0	0 (0)	0	0 (0)	0	0 (0)
	Severe Hypoglycaemia	6	6 (4.2)	2	2 (1.3)	1	1 (0.7)	0	0 (0)
	Site Infections	8	7 (4.9)	0	0 (0)	1	1 (0.7)	0	0 (0)
	other - specify	32	22 (15.3)	10	10 (6.6)	8	6 (4.2)	5	5 (3.3)
Device	Diabetic Ketoacidosis	1	1 (0.7)	0	0 (0)	1	1 (0.7)	0	0 (0)
	Pump Failure	4	3 (2.1)	0	0 (0)	0	0 (0)	0	0 (0)
	Severe Hypoglycaemia	2	2 (1.4)	0	0 (0)	0	0 (0)	0	0 (0)
	Site Infections	8	7 (4.9)	0	0 (0)	1	1 (0.7)	0	0 (0)
	other - specify	14	11 (7.6)	3	3 (2)	0	0 (0)	0	0 (0)
Carer error	Insulin administration error	1	1 (0.7)	4	4 (2.6)	0	0 (0)	0	0 (0)
	other - specify	5	2 (1.4)	0	0 (0)	1	1 (0.7)	0	0 (0)
Meter error	other - specify	3	3 (2.1)	1	1 (0.7)	5	4 (2.8)	2	2 (1.3)
Incidental illness	Insulin administration error	1	1 (0.7)	0	0 (0)	1	1 (0.7)	0	0 (0)
	other - specify	5	5 (3.5)	3	3 (2)	0	0 (0)	1	1 (0.7)
Other	Diabetic Ketoacidosis	1	1 (0.7)	0	0 (0)	1	1 (0.7)	0	0 (0)
	Insulin administration error	0	0 (0)	1	1 (0.7)	3	2 (1.4)	3	3 (2)
	Severe Hypoglycaemia	4	4 (2.8)	2	2 (1.3)	1	1 (0.7)	2	2 (1.3)
	other - specify	5	4 (2.8)	3	3 (2)	0	0 (0)	0	0 (0)

Child reported PedsQL (diabetes module) score at 12 months was available for 71% (CSII 104, MDI 104) but 26 children in each treatment group were too young to complete the questionnaire.

Adjusted mean difference at 12 months of 3.1 (95% CI -0.6 to 6.8) favoured CSII but the result was not statistically significant. Parents of participants (CSII 128/144, MDI 123/149) reported a statistically significantly higher score with CSII with adjusted mean difference 4.1 (95% CI 0.6 to 7.6). This result should be interpreted against meaningful differences being 5 points or more.³⁶

There were 4.3 (95% CI 0.6 to 8.0) more contacts with healthcare professionals per participant treated with CSII (21.2), using texts, e-mails and phone calls, than those treated with MDI (16.9). Mean total costs were higher by £1,863 (95% CI £1,620 to £2,137) for CSII than for MDI; with the majority of this difference (£1,177) due to the additional cost of consumables and device (undiscounted annualised cost £600 CSII versus £80 MDI) (Table 4). There was no significant difference in QALYs between CSII (0.910) and MDI (0.916) [difference in means of -0.006 QALYs (95% CI, -0.031, 0.018)]. The probability of CSII being more expensive and less effective than MDI was 0.69, with no likelihood of CSII being cost-effective at a threshold of £20,000 per QALY.

Table 4: Resource use in participants treated with CSII compared to MDI

	Cost [mean £ (95% CI)]		
Items of resource use	CSII	MDI	Difference
Device (pump* 4-year lifespan or 2 pen devices)	600 (596 to 606)	80 (80 to 80)	520 (516 to 526)
Consumables* (e.g. needles, infusion sets, reservoirs)	1841 (1826 to 1861)	664 (664 to 664)	1177 (1162 to 1197)
Insulin (prescribed)	422 (364 to 486)	482 (426 to 541)	-60 (-142 to 24)
Healthcare professional contacts (telephone calls, faxes, texts or e-mails)	138 (117 to 162)	108 (92 to 124)	30 (3 to 59)
Scheduled outpatients visits	434 (434 to 434)	434 (434 to 434)	0 (0 to 0)
Unscheduled outpatient visits	309 (272 to 346)	328 (292 to 366)	-19 (-71 to 33)
Inpatient stays costed from HRGs	387 (245 to 553)	219 (142 to 306)	168 (5 to 352)
Emergency Department visits	26 (16 to 39)	13 (8 to 19)	13 (2 to 27)
Other hospital e.g. ward visits	3 (1 to 7)	3 (1 to 5)	1 (-3 to 5)
Family doctor visits	71 (56 to 88)	57 (45 to 69)	15 (-5 to 35)
Home visits	106 (80 to 138)	83 (66 to 100)	23 (-9 to 59)
School visits	53 (43 to 64)	56 (44 to 69)	-3 (-19 to 13)
Concomitant medications	12 (8 to 17)	15 (8 to 23)	-2 (-12 to 6)
Total cost	4404 (4197 to 4642)	2541 (2412 to 2672)	1863 (1620 to 2137)

* 25% discount not included.

DISCUSSION

Principal findings

In this RCT of newly diagnosed paediatric T1D patients, CSII treatment was neither more clinically effective than MDI nor cost-effective by the standards of the NHS. This was consistent across centres and strengthens the lack of evidence to support CSII. There is evidence that glycaemic control in the first year of diagnosis is predictive of longer term outcomes,^{37,38} and this is likely to be a critical period of care. Partial recovery of insulin production during the first year of diagnosis may significantly alter the treatment paradigm compared to later in the course of T1D and our findings should not be applied beyond the first year of diagnosis.

Strengths and limitations of study

Our data are strengthened by a high retention rate and consistency of age, gender, ethnicity and deprivation between treatment arms. Furthermore, age, gender, ethnicity and deprivation did not differ between those who consented and those who declined to participate. Participants were recruited at diagnosis of T1D and core diabetes education and contact with health care professionals was balanced across treatment arms.

Our recruitment rate was lower than predicted and was strongly influenced by early treatment preference. The diagnosis of T1D has been associated with symptoms of posttraumatic stress disorder in parents,³⁹ and for some families it may not have been possible to contemplate randomisation to a new treatment so soon after diagnosis. Had we deferred recruitment, we may have achieved higher recruitment rates. At the point of randomisation, those randomised to treatment with CSII were significantly more likely to have received their preferred treatment and it is likely that we recruited a population of patients favouring CSII. This may explain the higher numbers switching from MDI to CSII during follow up. Examination of glycaemic control at the time of switching did not indicate poorer control. Future studies should examine how preference and disappointment may influence utilisation of randomised treatments.

The ITT analysis included all participants in the group they were randomised to while the per protocol analysis excludes participants with major protocol deviations which included switching method of delivery. This allows some consideration of the effect, and while both analyses were not significant the conclusions are robust. In addition, to account for participants that switched method of delivery the safety population analysed participants in the group to the method of insulin delivery at the time of the safety event.

The NPDA report improvements in glycaemic control from 2010/2011 (72mmol/mol England and 70mmol/mol in Wales) to 2016/2017 (64mmol/mol, both England and Wales).¹ During this period a number of national initiatives have been undertaken which are likely to have contributed to this sustained improvement. However, only 15% of patients treated with CSII and 20% of patients treated with MDI achieved an HbA1c within the target range at the end of the first year of treatment. Glycaemic control is poorer in the United Kingdom than in other European countries and North America where CSII is used more commonly,¹¹ leading to speculation that increased use of CSII may improve glycaemic control. The relative inexperience of NHS practitioners in CSII treatment could have obscured the potential benefits of this treatment. However, study sites were selected on the availability of a core set of trained and experienced staff. There was no evidence of a treatment effect over time, and block randomisation ensured balance between treatment arms. The development, validation, documentation and monitoring of an education package and treatment protocols would have strengthened the study. However, in the absence of robust evidence to inform the development of these protocols, this would have incurred significant additional cost and delays. Standardisation of educational packages is ideal, but it is important that these can be individualised to meet the needs of patients and their families. The pace at which education can be delivered to an unselected cohort of newly diagnosed patients will be more measured than education of selected patients experienced in the treatment of T1D, and it may be unrealistic to expect all families to achieve a high level of sophistication in CSII use. Additional education in the use of CSII may have reduced the prevalence of AEs in this arm and improved glycaemic control,

although this should be set in the context of the adult study, INPUT, which reported no effect of a structure education programme on glycaemic control in patients treated with CSII.⁴⁰

A large number of adverse events were reported in the study cohort, and this is consistent with the background population of patients with childhood T1D treated with CSII. The NPDA report that treatment with CSII increased the risk of being admitted to hospital in DKA by 23%, and of being admitted to hospital for reasons other than DKA or hypoglycaemia by 27%. CSII treatment did not confer benefit or increased risk from admission with hypoglycaemia.⁴¹

The speed of technological developments outpaces the time required to deliver a clinical trial. It may be argued that the findings of the SCIP trial are outdated: Technology has advanced, clinical teams have greater experience of CSII, and improved education programmes and psychological support equips patients and their families to manage this therapy more successfully with fewer adverse events. However, observational data from the most mature CSII services report benefits in HbA1c below thresholds felt to be clinically meaningful,^{9,13} taking no account of the effect of deprivation or ethnicity on clinical outcomes. Enhanced education and psychological support also has the potential to improve quality of life and clinical outcomes in patients treated with MDI. To improve the timeframes required to deliver the evidence development of a clinical trial platform should be considered.

Comparison with other studies

Our findings are consistent with those reported in a smaller RCT of newly diagnosed patients,⁹ and previous studies of patients with established T1D.^{10, 42-44} Authors of a systematic review of adult and paediatric patients concluded that CSII enabled superior glycaemic control and QoL than MDI with fewer episodes of hypoglycaemia, but cautioned that the inclusion of observational data may have introduced bias.⁴⁵

The reported effect of CSII on QoL and treatment satisfaction varies.^{10, 40-42} In our study, parents of participants treated with CSII reported a small, but significantly higher PedsQL score for the QoL of

their children. A qualitative approach may detect differences in QoL that were not identified in our questionnaire-based approach. No adjustments for multiplicity were applied to secondary outcomes and SCIPi was not powered to detect differences within these outcomes. Consequently, the results should not be judged solely by the presence or absence of statistical significance.

Tools for recording insulin use were less robust in those treated with MDI than CSII, and difficulties with data downloads from glucometers and pumps, and missing data in handheld records resulted in a large number of missing data. In contrast to previous studies,^{13,18,20} insulin requirements were higher in patients treated with CSII. This may reflect a reduction in the intensity of MDI treatment as older participants gain independence, or under reporting. Recognising this uncertainty, our data relating to partial remission should be interpreted with caution.

Conclusions and policy implications

Many patient advocacy groups and health care professionals are of the strong opinion that treatment with CSII is beneficial and further research should focus on determining what these perceived benefits are and to develop validated tools to measure them. Individual patients are likely to experience benefits from this treatment that are not directly associated with the outcomes measured in this study. For example, the preschool child who consumes carbohydrates and exercises erratically may benefit from a treatment with fewer injections and a basal insulin profile that can be modified readily. For the SCIPi cohort, longer term observation is required to assess how treatment in the first year has influenced the trajectory of glycaemic control in future years.

Evolving technology that automates glucose monitoring and insulin dose adjustment has the potential to reduce the burden of CSII therapy to patients and families, and enable superior glycaemic control to that reported in SCIPi participants. These technologies are likely to be considerably more expensive than those evaluated in this study and evidence should be sought to support their use.

In considering the outcomes of the SCIPi study it is important to recognise the following points (1) glycaemic control was suboptimal in both treatment arms (2) patients recruited to the study were

newly diagnosed and more favourable results may be achieved with CSII in patients more experienced in the treatment of T1D (3) advances in technology may reduce the burden of CSII therapy, and facilitate superior control in time.

In resource limited settings, it is important that the introduction of novel, expensive therapies is informed by robust clinical data demonstrating superiority. Data from the SCIP study demonstrate that the use of CSII was neither clinically beneficial nor cost effective in the first year of T1D, and resources may be more effectively invested in other measures to improve glycaemic control.

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The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

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Data Sharing

We are committed to sharing anonymised individual patient data for the purpose of research for the benefit of patients with bonefide researchers. Requests for data should be sent to the Clinical Trials Research Centre, University of Liverpool.

CONTRIBUTORS

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Chief Investigator and Consultant Paediatric Endocrinologist: Developed study protocol in collaboration with co-investigators. Oversaw the delivery of the study, prepared study update reports, oversaw clinical aspects of the statistical analysis plan, clinical interpretation of study data and led the preparation of the final report. Chair of Trial Management Committee.

Carrol Gamble

Senior Statistician: Contributed to the study design, protocol development, and data capture methods and led the CTU involvement. Contributed to the preparation of the manuscript (drafting, reviewing, editing)

Andrew McKay

Study statistician: Undertook the final statistical analyses under the supervision of Professor Gamble, prepared data for reports throughout the study, prepared data Tables and Figures for the manuscript. Contributed to the preparation of the manuscript (drafting, reviewing, editing). Member of Trial Management Committee.

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DECLARATION OF INTERESTS

ALL AUTHORS HAVE COMPLETED THE ICMJE UNIFORM DISCLOSURE FORM AT WWW.ICMJE.ORG/COI_DISCLOSURE.PDF. DETAILS OF INDIVIDUAL COMPETING INTEREST ARE GIVEN BELOW.

Joanne Blair: COMPETING INTERESTS: Professor Blair undertakes paid advisory work, has received funding for research, to attend academic meetings and to support a nursing salary from Novo Nordisk, a pharmaceutical company that manufactures some of the insulins used in the SCIPi study. The work undertaken by Dr Blair for this company relates to growth hormone therapy and not diabetes. **Andrew McKay:** COMPETING INTERESTS: NONE DECLARED, **Colin Ridyard:** COMPETING INTERESTS: NONE DECLARED, **Keith Thornborough:** COMPETING INTERESTS: NONE DECLARED, **Emma Bedson:** COMPETING INTERESTS: NONE DECLARED, **Matthew Peak:** COMPETING INTERESTS: NONE DECLARED, **Mohammed Didi:** Dr Didi has received payment for advisory work, funding to attend academic meetings and to support a nursing salary from Novo Nordisk, a pharmaceutical company that manufactures some of the insulins used in the SCIPi study. The work undertaken by Dr Didi for this company relates to growth hormone therapy and not diabetes. Dr Didi has received expenses from Merk Serono to attend educational meetings. **Francesca Annan:** COMPETING INTERESTS: NONE DECLARED, **John Gregory:** COMPETING INTERESTS: Chairmanship of the NovoNordisk UK Foundation, receipt of funding from NovoNordisk, Ipsen, Serono & Pfizer to part-support attendance at annual scientific meetings of the European Society for Paediatric Endocrinology & speaker's fees to talk on communication skills from Pfizer and Lilly, **Dyfrig Hughes:** COMPETING INTERESTS: NONE DECLARED, **Carrol Gamble:** COMPETING INTERESTS: NONE DECLARED

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